THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 23-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mitsuhashi *et al.* (U.S. Patent No. 4,659,569; "Mitsuhashi") and Sasaki *et al.* (JP 59-29831; "Sasaki"). Briefly, the Examiner contends that Mitsuhashi and Sasaki teach that embryonated eggs under 10-days-old are susceptible to viral infection and replication, particularly influenza viruses. Although the Examiner appreciates that neither of the cited references teach the "specific viral strains" of the claimed invention, according to the Examiner, it would have been *prime facie* obvious to one of ordinary skill in the art at the time of the invention, to apply the teachings of the cited references to make the composition of the claimed invention. According to the Examiner, one skilled in the art would have been motivated to do so because "it is notoriously old and well known in the art to propagate viruses in such eggs" and one would "reasonably expect the infected egg to yield replicated virus". For the reasons detailed below, this rejection cannot stand and should be withdrawn.

In order to expedite the prosecution of this application and without conceding to the merits of the Examiner's rejection, Applicants have canceled Claims 23-40, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have added new Claims 41-70 to more particularly point out and distinctly claim the subject matter of the invention. New independent Claims 41, 42, 44 and 45 (and claims dependent therefrom) are directed to embyronated eggs containing an attenuated negative strand RNA virus with impaired interferon antagonist activity. In particular, new independent Claim 41 recites an embryonated egg less than ten days old containing a recombinantly engineered attenuated negative strand RNA virus with impaired interferon antagonist activity, wherein said virus is not influenza C virus. New independent Claim 42 recites an embryonated egg less than ten days old containing a recombinantly engineered attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein said virus is not influenza C virus. New independent Claim 44 recites an embryonated egg containing in the allantoic cavity an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein the embryonated egg is six to nine

days old and said virus is not influenza C virus. New independent Claim 45 recites an embyronated egg less than 10 days old containing delNS1.

New independent Claims 58-60 (and claims dependent therefrom) are directed to interferon deficient cell lines containing an attenuated negative strand RNA virus with impaired interferon antagonist activity. In particular, new independent Claim 58 recites an interferon deficient cell line containing a attenuated negative strand RNA virus with impaired interferon antagonist activity, wherein said virus is not influenza C virus and the interferon deficient cell line is not Vero cells and is not Stat1(-) cell lines. New independent Claim 59 recites an interferon deficient cell line containing an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein the said virus is not influenza C virus and the interferon deficient cell line is not Vero cells and is not Stat1(-) cell lines. New independent Claim 60 recites an interferon deficient cell line containing delNS1, wherein the interferon deficient cell line is not Vero cells.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Appellants' disclosure. *In re Vaeck* 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Moreover, obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination", and "teachings of references can be combined only if there is some suggestion or incentive to do so." *In re Fine* 837 F.2d 1071, 1075 (Fed. Cir. 1988). It is impermissible to engage in hindsight reasoning, using the claims as a frame and the prior art reference as a mosaic to piece together a facsimile of the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* 220 USPQ 303, 312 (Fed. Cir. 1983).

None of the cited references, alone or in combination, teach or suggest the presently claimed invention. Mitsuhashi describes methods for production of virus vaccines utilizing 10-day-old embryonated eggs. Mitsuhashi also describes the propagation of Newcastle

disease virus in 8-day-old eggs. Sasaki describes a method for production of an inactivated influenza vaccine for pigs obtained by adding Macrogol, a polyethyleneglycol composition, to influenza viruses that are propagated in embryonated 9-11 day old egg allantois. Neither Mitsuhashi nor Sasaki teach, suggest or provide a motivation to one of skill in the art to propagate an attenuated negative strand RNA virus with impaired interferon antagonist activity in an embryonated egg less than 10 days old, let alone an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response in an embryonated egg less than 10 days old.

Further, as of the effective filing date of this application, the accepted age for inoculating embryonated eggs for the propagation of influenza virus was 10-12 days old. Thus, Applicants respectfully assert that one of skill in the art at the time of the invention would not have been motivated to propagate attenuated negative strand RNA virus with impaired interferon antagonist activity, in particular, attenuated influenza virus, in tissues such as the allantoic cavity of immature embryonated eggs, in particular embryonated chick eggs, less than 10 days old.

Applicants were the first to teach that immature embryonated eggs less than 10 days old (*e.g.*, six day old embryonated eggs) provide a better growth substrate for attenuated viruses with impaired interferon activity than older embryonated eggs (*e.g.*, 10 and 14 day old embryonated eggs) which are the conventional substrates for vaccine production. In particular, Applicants demonstrated that the allantoic cavity of immature embyonated eggs is an excellent growth substrate for attenuated influenza viruses having mutations in the NS1 gene that diminish or eliminate the ability of the NS1 gene product to antagonize the cellular interferon response. This result is particularly surprising because the allantoic cavity of immature embryonated eggs is very small and thus, not an obvious growth substrate to propagate virus to high titers. The cited art did not recognize or appreciate that immature embryonated eggs (*e.g.*, six day old eggs) are a better substrate for the propagation of an attenuated negative strand RNA virus with impaired interferon activity, in particular an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to induce a cellular interferon response. It was Applicants' unexpected discovery that attenuated influenza viruses having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to induce a cellular interferon response grow to higher titers in immature embryonated eggs that

resulted in the recognition of immature embryonated eggs as a suitable substrate for the propagation of attenuated negative strand RNA viruses with impaired interferon antagonist activity. Accordingly, Applicants respectfully assert that the cited references do not render presently pending Claims 41-57, directed to embyronated eggs, obvious.

Moreover, the cited references do not teach, suggest or provide a motivation to one of skill in the art to propagate an attenuated negative strand RNA virus with impaired interferon antagonist activity in an interferon deficient cell deficient cell line other than Vero cells, let alone an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response in an interferon deficient cell deficient cell line other than Vero cells. Mitsuhashi describes propagating a virulent measles virus in Vero cells. Sasaki only describes propagating influenza virus in embryonated eggs. Accordingly, Applicants respectfully assert that the cited references do not render presently pending Claims 58-70, directed to interferon deficient cell lines, obvious.

In view of the foregoing, Applicants respectfully submit that the rejection under 35 U.S.C § 103(a) cannot stand and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all of the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections is therefore respectfully requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-9090.

Respectfully submitted,

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